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A STUDY

OF THE

Comparative Actions of Antipyrine, Phenacetine and Phenocoll

ON THE

Circulation and Heat Phenomena.

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ON THE CIRCULATION.

We propose in this research, as the title indicates, to make a study of the comparative actions of antipyrine, phenacetine and phenocoll on the circulation, and particularly on heat phenomena.

Antipyrine and phenacetine have already been largely employed experimentally and clinically, with more or less asserted success as antipyretics, but we believe that a further study of these drugs, especially when compared with the new remedy, phenocoll, will be not amiss. We feel that the results of this investigation may form a stronger basis for the antipyretic use of these medicaments, particularly the latter one, in practical medicine.

As our study of the whole subject is directed especially to investigate the behavior of these drugs on heat phenomena, which we consider of greater importance as regards their use in the treatment of disease, we have not made, perhaps, an exhaustive inquiry into the physiological action of the drugs in question on the circulation. Let this statement serve as an excuse for any shortcomings that the critical physiologist may find in our conclusions. We fully believe, however, that the results obtained with each individual drug, following the various methods emyloyed and sufficiently described in the course of this article, sustain, so far, the correctness of the conclusions indicated below.

We have made an elaborate series of experiments on dogs, and the results observed are of such an interesting character as to warrant a serious consideration of the subject. We shall first take up the study of the actions of the drugs in question on the circulatory system, and then carefully consider their influence on heat phenomena in normal and fevered animals.

ANTIPYRINE.

How this drug acts on the circulation of mammals has not been definitely determined. The large mass of experimental evidence so far published is mainly contradictory, and without going into an elaborate examination of the literature on the subject, we will endeavor to point out the main conclusions arrived at by various investigators when considering separately the actions of the drug on the blood-pressure, the pulse, and the blood itself.

Blood-pressure.—Pavlinow [1]) has asserted that antipyrine causes a rise of the arterial pressure. Demme [2]) has observed the same result, this being followed by a fall notwithstanding the fact that the heart continued to act well. The same rise of pressure has been noticed by Arduin [3]), Devraux-Armand [4]) and Henry Casimir [5]), when small or moderate doses were employed. On the other hand, Simon and Hock—quoted by Wood [6])—Wood [7]), Hare [8]) and Dujardin-Beaumetz [9]) sustain that antipyrine in medicinal amounts has little or no effect upon the circulation. All authors agree more or less in that large quantities of this drug produce a depressant circulatory action; but aside from this contradictory evidence, no extended studies have been made to decide exactly how antipyrine influences the circulation, especially as regards the pulse and the blood-pressure.

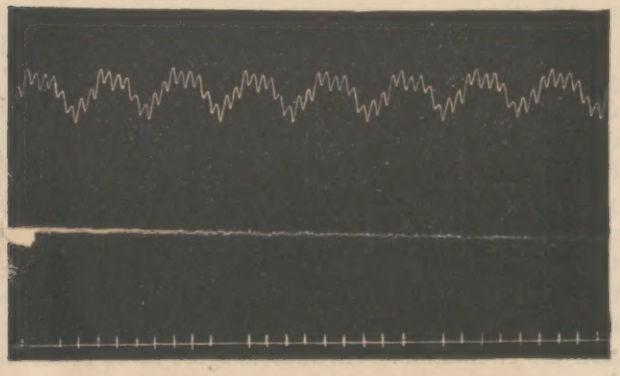
We have made several experiments on normal animals, with various doses, and observed that in small and moderate amounts the tendency of antipyrine is to increase the arterial pressure. We shall only detail two examples. In Experiment I the pressure rose above the normal height after the second dose, which also

[1]) Meditz. Obozr. fasc. XII, 1885, p. 1203.
[2]) Fortschritte der Medicin. Bd. II, 1884, p. 657.
[3]) Thése de Paris, 1885.
[4]) Thése de Nancy, 1885.
[5]) Thése de Lyon, 1886.
[6]) Therapeutics: Its Principles and Practice, Edition of 1891.
[7]) *Ibid.*
[8]) Fever: Its Pathology and Treatment, 1891.
[9]) Therapeutic Gazette, September 15, 1885.

produced convulsions, but these soon disappeared. The pressure continued high during the rest of the experiment, and, as is observed, no more convulsions occurred. The pressure only fell just before death. Although there was at first a slight diminution in the respiratory movements, these became increased in rate afterwards. The temperature remained *unaffected*, and in the final fatal issue both the respiration and heart stopped simultaneously.

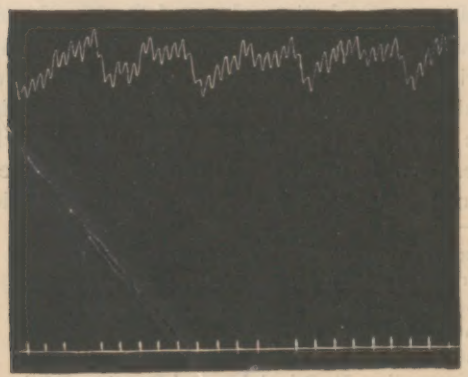
In Experiment II, in which comparatively larger amounts were employed, there was a fall after each injection, due, undoubtedly, to a direct depressant action of the drug upon the cardiac viscus, since such a fall was inevitably followed soon afterwards by the usual rise above the norm. The effect on respiration was similar to that of the first experiment, while the temperature was raised 0.2 of a degree before the occurrence of death, this taking place through failure of the respiration. We append these two experiments in tabular form as follows:

FIG. I. (Normal).*



ANTIPYRINE.—Tracing of a dog, weighing 14 kilos. Injected into jugular vein 30cc. of a 10 % in 3 equal doses, with intervals of 2 minutes.

FIG. II. (Normal.)



ANTIPYRINE.—The same, 1 minute after the last injection.

* All these tracings have been reduced to just *one-half* their original size.

EXPERIMENT I. *Normal.*

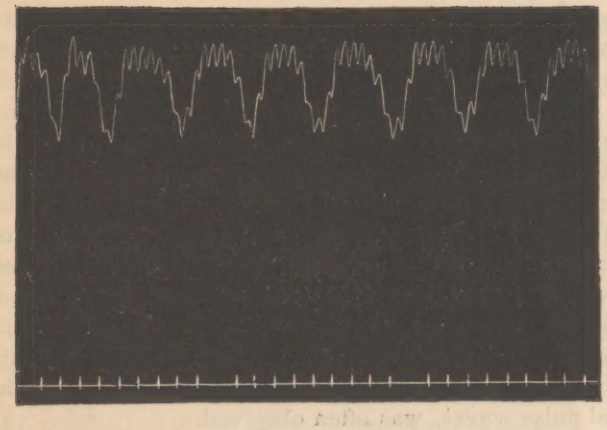
Time Min.	Time Sec.	Dose Grammes	Pulse per Min.	Pressure M.M.	Respiration per Min.	C° F	Remarks. Dog Wgt. 5.6 kilos.
0			120	140	57		39.6. *Antipyrine* Solution 10 per cent.
3	30	10cc.	120	140	57		Inj. begun into jugular vein.
4	00		120	140	57		Inj. ended.
10	30	20cc.	129	144	48		Inj. begun.
11	10		138	160	33		Convulsions.
11	40		141	170	30		Inj. ended.
12	30		150	190	42		39.6.
15	40	10cc.	159	174	72		Inj. begun.
16	10		159	180	48		Inj. ended.
16	40		174	190	42		
23	10	20cc.	174	170	60		Inj. begun.
24	10		159	170	60		Inj. ended.
24	40		153	192	—		39.6. Respiration irregular and shallow. From this on the pressure and pulse rate gradually fell till the occurence of death 3 minutes later. Respiration and heart stopped together.

EXPERIMENT II. *Normal.*

Time Min.	Time Sec.	Dose Grammes	Pulse per Min.	Pressure M.M.	Respiration per Min.	C° F	Remarks. Dog Wgt. 13.4 kilos.
0			132	130	15		39.8. *Antipyrine* Solution 10 per cent.
2	00	40cc.	132	130	15		Inj. begun into jugular vein.
3	00		123	134	12		
4	00		132	140	12		
5	00		141	150	12		Inj. ended.—Convulsions.
6	00		105	160	39		
7	00		132	160	18		39.7. Convulsions ceased.
13	00		135	150	12		
15	00	10cc.	144	140	21		Inj. begun.
15	20		144	140	18		Inj. ended.—Struggles.
17	20	10cc.	144	150	30		Inj. begun.
17	50		90	150	39		Inj. ended.
21	40	30cc.	132	150	15		Inj. begun.
22	40		78	170	42		Struggles.
23	40		150	180	27		Inj. ended.
24	00		120	220	18		
24	40	20cc.	132	200	18		Inj. begun.
25	40		129	210	15		Inj. ended.—Convulsions.
26	40		147	160	15		
27	40		129	180	12		
28	40		165	200	12		Convulsions.
29	30		159	200	15		39.9. Animal died from respiratory failure 2½ minutes later under another dose of 20cc.

We have found, in the course of our experimentation, that the fatal dose of this drug in dogs, intravenously injected, is 10 cc. of a 10 per cent. solution, or 1 gramme per kilo of the body weight.

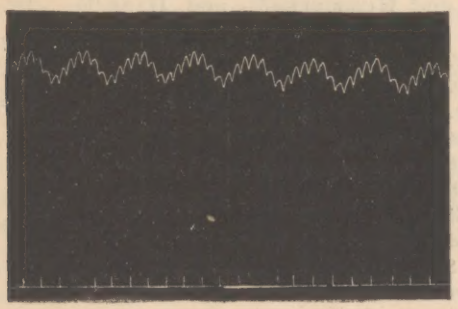
FIG. III. (Normal).



ANTIPYRINE.—The same. 5¾ minutes after the last injection.

In studying the cause of the rise of pressure we shall avoid an unnecessary lengthy discussion of the subject. We believe that the rise cannot be attributed to the convulsant action of antipyrine, or to changes in the respiratory function, since the same result is observed in curarized animals. In dogs under the influence of curare, and in which artificial respiration was kept up, thus preventing the occurrence of the said convulsant action of the drug, and, at the same time, any changes that might be due to respiratory disturbances, antipyrine produced phenomena similar to those effected in normal animals. This is proven by Experiment III, an example of others performed. In this experiment, it will be observed, there was a fall of pressure after each injection, but it was only temporary and due, without doubt, to a depressant action of the drug upon the heart. The lowering of the pressure was soon followed by a considerable rise above the normal point, accompanied, as in the case of normal experiments, by an increase in the rate of the heart beats, this being in itself of great significance. This is shown in the table given below.

FIG. IV. (Curarized).

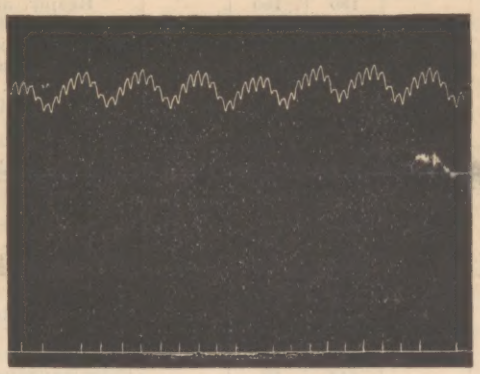


ANTIPYRINE.—Tracing of dog, weighing 10.5 kilos. After the animal was under the influence of curare, injected 30 c. c. of 10 % solution, in 3 doses, with an interval of 5 minutes.

EXPERIMENT III. *Curarized.*

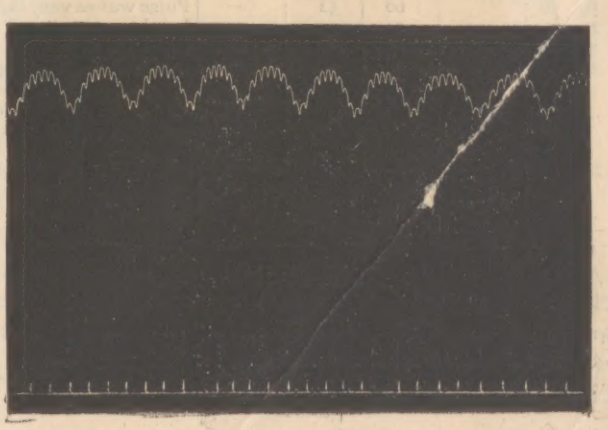
Time Min.	Time Sec.	Dose Grammes	Pulse per Min.	Pressure M.M.	Respiration per Min.	Remarks. Dog Wgt 9.29 kilos.
0			96	130		Antipyrine. 10 per cent. Solution.
1	00	10cc.	96	130		Inj. begun into jugular vein.
2	00		93	100		Inj. ended.
5	30	40cc.	99	130		Inj. begun.
6	30		105	130		
7	30		105	130		
8	30		120	140		Inj. ended.
16	00	20cc.	156	180		Inj. begun.
17	10		144	160		Inj. ended.
17	50		123	140		
24	30	60cc.	156	184		Inj. begun.
25	30		141	130		
26	30		117	116		
27	30		120	120		
28	30		114	100		Inj. ended.
39	30	50cc.	183	200		Inj. begun.
40	30		144	150		
41	30		129	110		
42	30		129	100		
43	30		117	90		Inj. ended. Pulse waves large.
49	00		135	90		Animal died under another dose of 40cc. 2 minutes later.

FIG. V. (Curarized).



ANTIPYRINE.—The same, 6 minutes after last injection. Eight minutes after gave 30cc. of same solution, in the course of 2 minutes.

FIG. VI. (Curarized).



ANTIPYRINE.—The same, 15 minutes after the third injection

Identical results in regard to the arterial pressure were obtained in animals whose vagi had been previously cut, and, similarly, in those in which both the pneumogastrics and spinal cord had been severed, with the application, in these latter instances, of artificial respiration. The following experiments, detailed in tabular form, are self-explanatory:

EXPERIMENT IV. *Vagi Cut.*

Time Min.	Time Sec.	Dose Grammes	Pulse per Min.	Pressure M.M.	Respiration per Min.	C° F°	Remarks. Dog Wgt. 28.117 kilos.
0			225	170		39.6.	*Antipyrine* Solution 10 per cent.
10	30	20cc.	225	170			Inj. begun into jugular vein.
11	10		213	170			Inj. ended.
12	10		201	176			
15	40	20cc.	192	170			Inj. begun.
16	20		186	170			Inj. ended.
17	50		189	190		39.	
22	00	20cc.	177	170			Inj. begun.
22	40		168	130			Inj. ended.
28	00		174	190			
28	50		174	180		38.	Respirat. frequent.
34	20	30cc.	174	174			Inj. begun.
35	40		150	150			Inj. ended. Animal struggles. Respirat. about 60 per minute.
44	10		186	160			Respir. about 100 per minute.
49	10		171	180		38.	Quiet again; respiration about 10 per minute. Killed afterwards with ether.

EXPERIMENT V. *Cord and Vagi Cut.*

Time Min.	Time Scc.	Dose Grammes	Pulse per Min.	Pressure M M.	Respiration per Min.	Remarks. Dog Wgt. 9.2 kilos.
0			168	44		*Antipyrine.*
15	00	4 grm.	168	44		Inj. begun into jugular vein.
16	00		162	44		
17	00		144	50		Pulse waves very large.
17	50		135	50		Inj. ended.—Pulse waves large. Convulsions.
18	50		45	36		Pulse waves very large.
19	50		60	32		Pulse waves very large.
22	50	1 grm.	54	50		Inj. begun.
23	20		162	50		Inj. ended.
23	50		—	—		Heart entirely stopped for 10 seconds and it then began to beat again; pulse waves very large.
24	50	3 grm.	39	30		Injected at short intervals, the heart being finally paralized in diastole.

It is evident from these results, that antipyrine exercises no apparent influence on the vaso-motor system, and that its stimulating effect upon blood-pressure, when adminstered in small and moderate doses, is chiefly, if not wholly, of a cardiac origin.

It is perhaps needless for us to add that the reduction of the arterial pressure produced by antipyrine, under large and toxic amounts, is, independent of the vaso-motor apparatus, also due to a depressant action of the drug upon the heart.

The Pulse.—As will be noticed from the experiments on normal animals, the rate of the pulse, *pari passu* with the rise of the pressure, was generally increased. Sometimes there would occur a primary decrease, especially after the injection, due, probably, to an overwhelming action of the drug upon the heart; this decrease, however, was soon recovered from, followed by the usual increase above the normal rate. A more or less permanent secondary diminution in the number of heart beats, accompanied with a markedly large size of the individual pulse waves, was often observed.

After previous division of the pneumogastrics antipyrine, with a single exception, was unable to increase the rapidity of the heart. The drug, on the contrary, under such conditions, produced a reduction of the pulse-rate. Similar phenomena were obtained (as an examination of the experiments shows) when all nerve-supply to the heart was cut off by previous section of the vagi and the spinal cord. These results lead us to the conclusion that the primary rapid pulse is due to paralysis of the cardio-inhibitory centres; the secondary decrease to an action upon the heart itself.

Antipyrine does undoubtedly exercise, in sufficiently large doses, a direct depressant influence upon the heart of mammals, in the same way as it does upon that of the frog according to the observations of ARDUIN [1]), DEMME [2]), HARE [3]), FAVAL [3a]), and BATTEN and BOKENHAM [4]), although this is denied by COPPOLA [5]). The organ is generally arrested in diastole, and this we have confirmed by post-mortem examination in some of the animals killed by the drug.

The Blood.—We have never been able to notice any changes in the character of the blood produced by antipyrine when administered in comparatively small or medicinal doses. This appears to be in accord with the observations of ARDUIN [6]), PAVLINOW [7]) HUCHARD [8]) CROLAS and HUGOUNENQ [9]), and HARE [10]). In large or

1) *Loc. citat.*
2) *Loc. citat.*
3) *Loc. citat.*
3a) Thése de Lyon, 1887.
4) British Medical Journal, June 1. 1890.
5) Kobert's Jahresbericht, p. 314, 1885.
6) Bull. General. de Therap., March 30, 1885.
7) Meditz. Obozr. fasc. XII, p. 1203, 1885.
8) La Semaine Medicale, March 3, 1889.
9) Lyon Medicale, March 3, 1889.
10) *Loc. citat.*

toxic amounts antipyrine produces (and this we have sometimes observed) a chocolate color of the blood, which is probably due to an alteration of the haemoglobin into methaemoglobin. LEPINE [1]) affirms, after a careful spectroscopic examination of the blood of animals poisoned by antipyrine, that such changes occur, an observation upheld by HARE and others, and apparently sustained by a large mass of clinical evidence.

In regard to the corpuscular elements, these undergo no appreciable change, according to CROLAS and HUGOUNENQ [2]) and PISEMSKI [3]), who have made special researches on this point. The latter author states that ultimately the blood corpuscles may be diminished in number, but believes that such a phenomenon results, not through a direct action exercised by antipyrine, but from exhaustion of the animal experimented upon.

We are in accord with the preceding statements, and there is scarcely any doubt that they are entirely correct.

We may state in passing, that as regards the respiratory function, this was markedly increased even by small doses of antipyrine, and since this stimulation occurred similarly after previous division of the pneumogastric nerves, it is safe to assume that it is due to a direct action of the drug upon the respiratory centres in the medulla oblongata. The temperature in normal dogs, as the records show, was practically *unaffected*; but we shall return to this when we especially treat of heat phenomena.

CONCLUSIONS.—A summary of the actions of antipyrine on the circulation is now given:

1. Antipyrine in small and moderate amounts produces a rise of the arterial pressure, this stimulating effect being due to an action upon the heart.

2. The lowering of the pressure by large or toxic doses is due similarly to a depressant action of the drug upon the cardiac organ. The remedy does not seem to influence the vaso-motor system.

3. Antipyrine causes an increase in the pulse-rate through paralysis of the cardio-inhibitory centres. The secondary decrease in the number of pulsations is of a purely cardiac origin, the drug exercising a depressant effect upon the heart itself.

4. Antipyrine, in excessive doses only, changes the haemoglobin of the blood into methaemoglobin.

PHENACETINE.

The literature concerning the study of the actions of phenacetine upon the circulatory system is almost *nil*. The first investigators to study the general action of the drug were HINSBERG and KAST [1]), yet they did not make a thorough research regarding the influence that this remedy exercises upon the circulation. The authors just quoted found, among other effects produced upon the nervous system and respiration, that phenacetine caused cyanosis and discoloration of the blood, attriubuting this phenomenon to the conversion of haemoglobin into methaemoglobin. OTT [2]) in studying the actions of phenacetine upon heat phenomena, has asserted that this drug causes, while distinctly decreasing heat production, no alteration of the blood-pressure. HARE [3]) who has experimented with the remedy quite extensively, affirms likewise that phenacetine acts with comparatively little power upon the circulation, and that even very large doses do not influence the pulse-rate and the blood-pressure.

We dissent from these views, and we cannot understand how such an able investigator and careful observer as HARE has failed to obtain the sufficiently marked effects that we believe the drug under consideration produces upon both the blood-pressure and pulse, judging from the results of the experiments that we shall presently detail. Phenacetine is an insoluble substance, and we do fear that HARE did not inject into the animal the quantity supposed to have been administered. Such has happened to us in many instances, especially when the canula connected with the vein would be so small as to be easily occluded by the undissolved drug, and it was under such circumstances that no apparent effect could be noticed on the circulation.

Several experiments were performed with a view to ascertain the actions of phenacetine on blood-pressure and pulse in normal animals, but only some of the most striking of said experiments will be detailed.

The Blood-pressure.—For Exp. I a dog weighing 9.9 kilos was employed, administering, in varying amounts, a 2 % solution of the drug. After the first injection of 10 cc. the normal pressure which was 136 mm. was elevated to 140 by the end of the injection, which occupied 40 seconds. The column of mercury in the manometer soon returned to normal. Subsequent injections produced identical results, the pressure remaining above the normal for a period of fully 39 minutes, during which seven doses of from 10 to 40 cc. each were given at intervals of from 1 to 11 minutes. The respiration was not observed. The temperature was increased 0.2 of a degree by the end of the experiment.

[1]) Lyon Medicale, Vol. III.
[2]) *Loc. citat.*
[3]) St. Petersburg Inaugural Dissertation, p. 48, 1887.

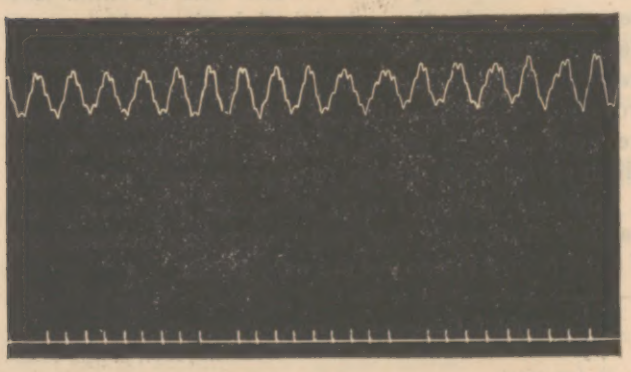
[1]) Centralbl. f. Gesammt. Therap., April, 1887.
[2]) Journal of Nervous and Mental Diseases, XV., p. 598, 1888.
[3]) *Loc. citat.*

In Exp. II a 5 % solution was used in a dog weighing 20 kilos. In this instance the first injection of 10 cc. produced a fall of pressure, but such was recovered from in 5 minutes. No change followed a second dose of the same amount. There was a slight reduction after the third injection of a similar quantity, the pressure returning to the original point in the course of 3 minutes. Three other doses of 20 cc. each caused a fall, the pressure never going back to the norm. The respiration was decreased in rate, and only slightly increased after the sixth dose of 20 cc. No record was taken of the temperature.

For Exp. III a dog weighing 28 kilos was selected. Each of the four one-gramme doses was followed by an increase of the arterial pressure. The fifth injection of 4 grammes caused a fall which was gradual till the occurrence of death, this being preceded by a tetanic convulsion. The respiratory function was unaffected after the third, and more so after the fourth dose. It became markedly rapid at the beginning of the fifth large dose, stopping finally two minutes afterwards, while the heart continued to act for 1½ minutes longer. Death resulted, therefore, from respiratory failure. The temperature was reduced 0.4 of a degree.

A small dog weighing 5.8 kilos was used for Exp. IV. A lowering of the pressure occurred immediately after the single injection of one gramme, and so continued for about six minutes. It then returned to 120 mm., the normal height being 130 m. In the course of three minutes longer there was a sudden fall of pressure and the animal ceased breathing, while the heart continued to beat for two minutes later when it also stopped. The respiration, though irregular, was increased in rate, and before death it became markedly shallow. Failure of the respiratory function was the cause of death. The temperature was diminished 1.3 of a degree.

FIG. a. (Normal).



PHENACETINE.—Tracing of Dog, weighing 28 kilos. Gave intravenous injection of 1 gramme of drug, suspended in water

It is thus seen that in two of these experiments, in which comparatively moderate quantities of phenacetine were employed, the arterial pressure was increased. In the other two instances in which larger and toxic amounts were ingested, the pressure was notably decreased, and so continued till the final fatal effect.

The lethal dose of phenacetine, intravenously administered, we have calculated to be 0.26 grammes per kilo of the body-weight of the animal.

We accompany the preceding experiments in tabular form, as follows:

EXPERIMENT I. *Normal.*

Time Min.	Time Sec.	Dose Grammes	Pulse per Min.	Pressure M.M.	Respiration per Min.	Temp. C°	Remarks. Dog Wgt. 9.9. kilos.
0			126	136		39.7.	*Phenacetine* Solution 2 per cent.
2	00	10cc.	126	136			Inj. begun into jugular vein.
2	40		156	140			Inj. ended.
3	20	20cc.	126	136			Inj. begun.
4	20		120	144			Inj. ended.
7	20	30cc.	126	140			Inj. begun.
9	20		78	150		39.7.	Inj. ended.
11	40		150	150			
14	10	20cc.	—	—			Inj. made.
18	00		126	150			
20	30	20cc.	108	140			Inj. made.
22	00		108	148			
25	30	20cc.	114	140			
26	40		132	154			
28	00		126	146		39.9.	
33	00		—	—			Animal vomits and defecates.
36	00	40cc.	114	140			Inj. begun.
39	00		96	140			Inj. ended.
							Animal died under another dose of 10cc. 3 minutes later.

EXPERIMENT II. *Normal.*

Time Min.	Time Sec.	Dose Grammes	Pulse per Min.	Pressure M.M.	Respiration per Min.	Remarks. Dog Wgt. 20 kilos.
0			93	160	30	*Phenacetine* Solution 5 per cent.
0	50	10cc.	93	160	30	Inj. begun into jugular vein.
1	30		99	148	30	Inj. ended.
2	10		159	150	30	
5	40	10cc.	177	160	15	Inj. begun.
6	10		168	160	14	Inj. ended.
7	10	10cc.	165	160	15	Inj. begun.
7	40		165	150	15	Inj. ended.
8	10		174	160	18	
10	40	20cc.	141	160	12	Inj. begun.
11	40		102	120	18	Inj. ended.
12	20		96	150	21	
22	20	20cc.	132	156	15	Inj. begun.
23	10		132	144	15	Inj. ended.
24	00		147	156	24	
25	30	20cc.	132	156	24	Inj. begun.
26	20		105	140	36	Inj. ended.
						Same result followed under another injection of 10cc. Animal was afterwards killed with ether.

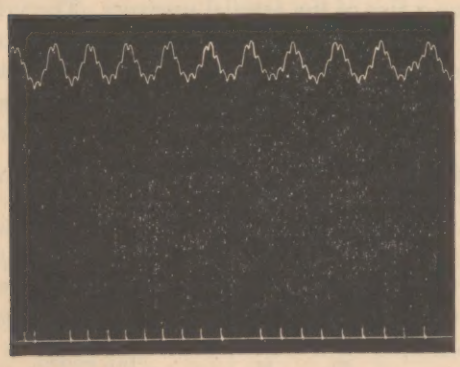
EXPERIMENT III. *Normal.*

Time Min.	Time Sec.	Dose Grammes	Pulse per Min.	Pressure M.M.	Respiration per Min.	T. °C.	Remarks. Dog Wgt. 28 kilos.
0			174	136	33	40.3.	*Phenacetine.*
0	30	1 grm.	174	136	33		Inj. begun into jugular vein.
1	20		144	136	33		Inj. ended.
2	10		144	140	33		
6	40	1 grm.	180	144	27		Inj. begun.
7	30		180	140	27		Inj. ended.
8	10		180	144	27	40.	
11	40	1 grm.	132	144	33		Inj. begun.
12	20		144	144	36		
13	00		138	150	36		Inj. ended.
15	30	1 grm.	108	150	42		Inj. begun.
16	20		63	136	45	39.9.	Inj. ended.
19	20		111	140	18		
20	20		72	150	54		
25	50	4 grm.	180	150	111		Inj. begun.
26	30		144	136	99		
27	00		96	110	45		Inj. ended.
27	50		129	140	21		Tetanic Convuls.
28	30		150	70	—		Respir. stopped.
29	00		52	30	—		Heart ceased 1½ minutes later.

EXPERIMENT IV. *Normal.*

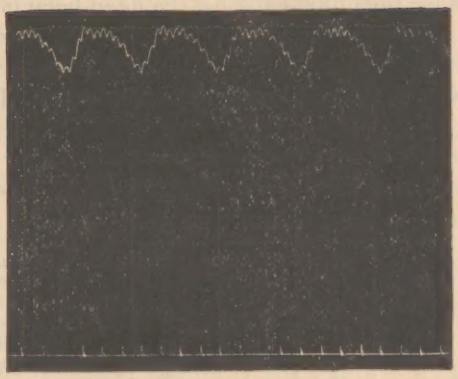
Time Min.	Time Sec.	Dose Grammes	Pulse per Min.	Pressure M.M.	Respiration per Min.	T. °C.	Remarks. Dog Wgt. 5.896 kilos.
0			105	130	24	38.8.	*Phenacetine.*
1	00	1 grm.	105	130	24		Inj. begun into jugular vein.
1	30		99	52	27		Inj. ended.
2	30		96	48	33		
4	30		15	24	42	38.	Respiration irregular; pulse waves large.
5	30		45	48	36		
6	40		84	120	—	37.5.	Respir. shallow; almost imperceptible.
7	40		15	—	—		Respir. stopped; heart continued to beat for two minutes longer, when it ceased.

FIG. b. (Normal).



PHENACETINE.—The same, 7 minutes after injection

FIG. c. (Normal).



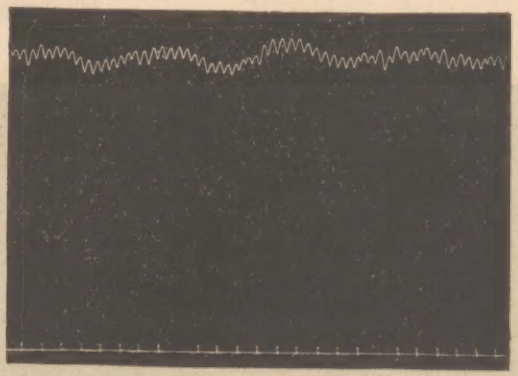
PHENACETINE.—The same, 5 minutes after last record, or 12 minutes after injection.

The results of the following experiment performed in a curarized dog, shows that, under such circumstances, phenacetine is still able to elevate the arterial pressure:

EXPERIMENT V. *Curarized.*

Time Min.	Time Sec	Dose Grammes	Pulse per Min.	Pressure M.M.	Respiration per Min.	Remarks. Dog Wgt. 15.873 kilos.
0			150	154		*Phenacetine.*
5	00	1 grm.	150	154		Inj. begun into jugular vein.
6	00		171	166		Inj. ended.
6	40		171	166		
7	40		165	170		
11	10		147	170		
16	10	1 grm.	183	160		Inj. begun.
17	10		195	160		Inj. ended.
17	50		201	164		
22	20	1 grm.	207	160		Inj. begun.
23	40		222	170		Inj. ended.
24	40		249	156		
27	10	2 grm.	246	156		Inj. begun.
28	10		246	130		Inj. ended.
28	40		264	120		
36	40		264	140		Killed afterwards with ether.

FIG. d. (Curarized).



PHENACETINE.—Tracing of Dog, weighing 22 kilos. After the animal was under the influence of curare, injected 1 gramme of drug.

Furthermore, an increase of pressure is observed in dogs whose pneumogastric nerves have been previously divided. This is shown in the following two experiments in which at the same time an increase in both the pulse and the respiratory rate also occurred:

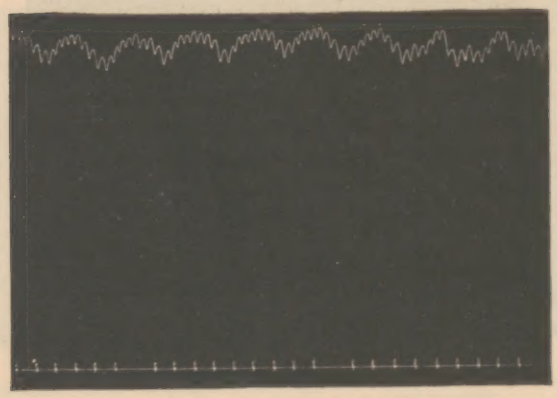
EXPERIMENT VI. *Vagi Cut.*

Time Min.	Time Sec.	Dose Grammes	Pulse per Min.	Pressure M.M.	Respiration per Min.	T. °C.	Remarks. Dog Wgt. 11.791 kilos.
0			165	146	306	40.2.	*Phenacetine.*
11	00	1 grm.	165	146	306		Inj. begun into jugular vein.
11	50		174	60	327		Inj. ended.
12	20		222	136	195		Respir. deeper.
12	50		213	204	390		Respir. shallow.
13	40		189	202	405	39.7.	
16	20	1 grm.	192	196	360		Inj. begun.
17	00		241	120	342		Inj. ended.
18	00		222	204	390		Respir. shallow.
18	50		249	176	180	38.1.	Respir. deeper.
24	20		213	210	360		Respir. shallow.
30	20	1 grm.	219	178	330		Inj. begun.
31	00		228	140	294		Inj. ended.
31	50		249	160	210		
32	10	1 grm.	249	160	210		Inj. begun.
33	00		249	140	150		Inj. ended.
33	40		231	166	—		Respir. almost imperceptible.
36	10		222	176	288		Died under a 2 grm. dose; heart and respir. stopped simultaneously.

EXPERIMENT VII. *Vagi Cut.*

Time Min.	Time Sec.	Dose Grammes	Pulse per Min.	Pressure M.M.	Respiration per Min.	T. °C.	Remarks. Dog Wgt. 5 891 kilos.
0			180	140	18	39.50.	*Phenacetine.*
11	00	0.5 grm.	180	140	18		Inj. begun into jugular vein.
11	50		180	110	27		Inj. ended.
12	50		180	130	48		
16	20		204	160	51		
18	00		216	160	30	38.8.	
21	30	0.5 grm.	210	146	198		Inj. begun.
22	10		201	104	210		Inj. ended.
23	00		201	114	102		
24	30		209	136	60		
26	30		219	144	60	38.6.	
31	30		216	136	39		Was afterwards killed with ether.

FIG. e. (Curarized).

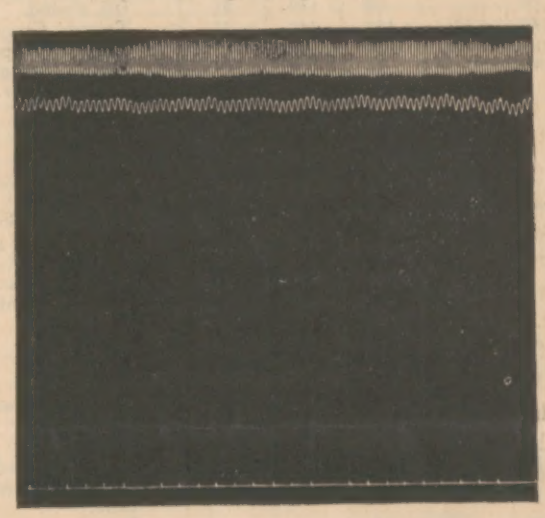


PHENACETINE.—The same, 5½ minutes after injection.

FIG. f. (Vagi Cut).

PHENACETINE.—Tracing of Dog, weighing 12 kilos. Injected 20 minutes after section of vagi, 1 gramme of drug, intravenously.

FIG. g. (Vagi Cut).



PHENACETINE.—The same, 3 minutes after injection. Uppermost line represents the respiratory movements.

In animals in which the spinal cord and the vagi have been previously severed, thus cutting off all nerve supply to the heart, with the complete production of vaso-motor paralysis, phenacetine was no longer able to produce a rise of the arterial pressure. The fall which the drug caused under such circumstances was recovered from in the course of a few minutes, but the pressure never went beyond the normal point. The following example explains itself:

EXPERIMENT IX. *Cord and Vagi Cut.*

Time Min.	Time Sec.	Dose Grammes	Pulse per Min.	Pressure M.M.	Respiration per Min.	Remarks. Dog Wgt. 6.4 kilos.
0			102	46		*Phenacetine.*
6	50	1 grm.	96	36		Inj. begun into jugular vein.
7	20		99	34		Inj. ended.
8	20		96	24		
9	00	0.5 grm.	96	24		Inj. begun.
9	20		93	12		Inj. ended.
						Heart stopped a minute later.

A study of these results, with the significant fact before us that the rate of the pulse and the column of the arterial pressure run a similar course, that is, increasing and diminishing together, would seem to show that both the rise and fall of the pressure are mainly of a cardiac origin. On the other hand, however, the failure of phenacetine to elevate the pressure after section of the spinal cord, would indicate that in part at least the drug exercises, in normal animals and under moderate doses, a stimulating influence on the vaso-motor system. The fall of pressure produced by the remedy in large or toxic doses, is due chiefly to an action upon the heart itself.

The Pulse.—An examination of the preceding experiments shows that, although in an irregular manner, the tendency of the drug in question is to produce, in more or less ordinary doses, an increase in the rapidity of the pulse. This rapidity is followed by a decrease in rate, though the force is sometimes manifestly increased as is attested by the large size of the individual pulse-waves, especially when larger amounts of the drug are adminstered. After the vagi have been previously divided the increased pulse-rate persists, but no secondary diminution is observed unless very late in the poisoning when overwhelming quantities of the drug have been ingested. It is apparent, then, that small and moderate doses of phenacetine increase cardiac action by influencing the heart itself, and that large amounts stimulate the cardio-inhibitory apparatus and thus cause a reduction of the pulse-rate.

But the inability of the drug to produce the usual increased pulse-rate after the heart has been deprived of all its nerve-supply, as is noticed in the example given, would seem to raise the question as to whether another factor must be taken into consideration for the explanation of the first result, that is, as to whether the drug, besides acting upon the heart itself, also stimulates the cardio-accelerating nerve apparatus. It is so difficulty to decide positively how drugs influence, if they do at all, the accelerating centres, owing to the passive condition of these as regards activity, that we have deemed it wise to leave the point at issue in the present instance in *statu quo*, the clearing up of which is reserved to more thorough future researches. There appears to be no doubt, however, that phenacetine in large quantities reduces the pulse-rate by a double action: stimulation of the cardio-inhibitory centres and, later, depression of the heart itself.

The Blood. — Although some observers, notably Hingsberg and Kast [1]), have stated that phenacetine alters the character of the blood, we have not, in our experimentation, been able to notice such phenomenon. The authors just cited claim to have proven, by spectroscopic analysis, that the dark color of the blood caused by the drug is due to the presence of methaemoglobin. Hare [1]) concurs in the same opinion.

Among other actions of the remedy under consideration, the most prominent is that exercised upon the respiratory function. Ordinary amounts produce no effect; but large quantities cause a marked quickening of the respiratory movements. As the same results take place after previous section of the vagi (see Fig. g.), it is evident that the drug acts directly upon the centres of the medulla. Death by phenacetine is caused by respiratory failure. The temperature in normal animals was reduced more markedly than in the case of antipyrine; this action will be more fully discussed later.

Conclusions.—We will now give the main conclusions regarding the actions of phenacetine upon the circulation, as found in the substance of the preceding discussion:

1. Phenacetine, in moderate doses, causes a rise of the arterial pressure by acting upon the heart, and probably likewise by a stimulating influence exercised on the vaso-motor system.

2. The reduction of pressure by the drug in large amounts is mainly of a cardiac origin.

3. The remedy increases in small doses the force of the heart by a direct action.

4. Phenacetine increases the pulse-rate chiefly by cardiac stimulation, and possibly also by influencing the cardio-accelerating apparatus.

5. The drug reduces the number of pulsations, especially in large quantities, primarily by stimulating the cardio-inhibitory centres, and, later, by a depressant action upon the heart.

PHENOCOLL.

This substance is a white, crystalline powder. It is soluble in water at a temperature of 62° F., in the proportion of 1 to 16 parts. It is more soluble in hot water and alcohol, but barely in chloroform, ether or benzol. Phenocoll is closely related to phenacetine, and is prepared by the interaction of para-amidophenotol (phenetidin) and amido-acetic acid (glycocoll). Acording to chemists phenocoll is represented by this formula:

$$C_6H_4 \begin{cases} OC_2H_5 \\ NH.COCH_2NH_2 \end{cases} + H_2O.$$

It is claimed that its ready solubility is due to the presence of the amide (NH_2) group. The new remedy has already been tried clinically, as an antipyretic, anti-

[1]) *Loc. citat.*

[1]) *Loc. citat.*

neuralgic, anti-influenzic, and anti-rheumatic, with asserted flattering success. Favorable reports have been published especially by HERTEL [1]), JACOBI [2]), HERZOG [3]), CONHEIM [4]), ALBERTONI [5]), BRADENBURG [6]), and others.

KOBERT and Von MERING, referred to in the *British Medical Journal*, Supplement, May 2, 1891, have asserted that the drug is non-poisonous to the lower animals, and that it exercises no deleterious influence upon the blood itself. The only attempt, however, at an experimental investigation with the new remedy, and with which we are acquainted, is that of OTT [7]). Unfortunately, the research of this able investigator is too brief, although apparently some of the conclusions arrived at in the preliminary note published by him are in accord with those which we have been able to formulate as the result of our experimentation with the drug under study.

Our experimentation with this drug (we have employed the *hydrochloride*, the salt generally used in practical medicine) has been carried on in a more extended scale than in the case of antipyrine and phenacetine, but to avoid an unnecessary prolixity, we shall submit to the consideration of the reader our most striking records. We will state from the start that the action of phenocoll upon the circulation, unless it be in enormous amounts, is not a marked one. As our aim, however, is to find how it acts upon the system when given in sufficiently large doses, the results we now publish represent more or less those produced by the drug when ingested beyond its therapeutic limit. We verily believe that in ordinary medicinal quantities phenocoll exercises, if at all, a slightly stimulating effect upon the circulation, and when it causes a depressant action, it does so in excessive amounts only. But how the changes we have just referred to are brought about, in other words, how phenocoll, and in what limitations as regards dosage, is able to impress the circulation, will be pointed out, as accurate as possible, in the following experimental discussion.

The Blood-pressure.—A dog weighing 10.231 kilos was used for Exp. I. The solution of phenocoll employed was of the strength of 4 %. After the first injection of 12 cc. the pressure fell, but soon returned to the norm. The same result was noticed after the second dose of the same amount. Under a third dose of 20 cc., injected 17 minutes afterwards, the pressure was reduced, and continued to go down till the occurrence of death. The respiration was comparatively unaffected, but somewhat shallow and diminished in frequency. The temperature was lowered only just before death. No change was observed in the character of the blood. Death was produced by respiratory failure.

EXPERIMENT I. *Normal.*

Time Min.	Time Sec.	Dose Grammes	Pulse per Min.	Pressure M M.	Respiration per Min.	C° F°	Remarks. Dog Wgt. 10.231 kilos.
0			156	150	30	39.4.	*Phenocoll* Solution 4 per cent.
0	40	12cc.	156	150	30		Inj. begun.
1	10		142	130	30		
1	40		150	66	30		Inj. ended.
2	00		129	50	27		Respir. shallow.
2	30		116	60	26		
8	00		135	100	27		
10	30	12cc.	159	150	30		Inj. begun.
11	00		160	90	26		
11	20		144	40	24		Inj. ended.
12	00		120	56	27		Respir. shallow.
13	30		132	88	30		
17	20	20cc.	148	150	30	39.2.	Inj. begun.
18	20		144	80	30		Inj. ended.
18	50		144	80	30	38.2.	Died 2 minutes later. Respir. fl.

EXPERIMENT II. *Normal.*

Time Min.	Time Sec.	Dose Grammes	Pulse per Min.	Pressvre M.M.	Respiration per Min.	Remarks. Dog Wgt. 12.698 kilos.
0			141	170	39	*Phenocoll* Solution 4 per cent. Prepared one of the vagi.
0	40	5cc.	141	170	39	Inj. begun.
1	10		180	100	33	Inj. ended.
1	40		183	160	33	
2	10		192	160	36	Stim. of central end of cut vagus; no response.
2	50	6cc.	180	170	27	Inj. begun.
3	20		174	120	30	Inj. ended.
3	30		180	160	36	
4	00		180	160	30	Another inj. of 10cc. produced death from respiratory paralysis.

EXPERIMENT III. *Normal.*

Time Min.	Time Sec.	Dose Grammes	Pulse per Min.	Pressure M.M.	Respiration per Min.	C° F°	Remarks. Dog Wgt. 18.140 kilos.
0			204	120	33	40.7.	*Phenocoll* Solution 4 per cent.
1	00	16cc.	204	120	33		Inj. begun.
1	30		171	84	33		
1	50		156	70	33		Inj. ended.
2	30		165	96	27		Respir. shallow.
8	00	16cc.	195	120	24	40.	Inj. begun.
9	00		123	70	15		Inj. ended.
9	30		122	30	16		
10	00		114	20	—		Respir. ceased.
10	30		54	20	—		Pulse waves large.
11	00		54	20	—		Pulse waves large. Heart ceased one minute later.

[1]) Deut. Med. Wochenschr., April 9, 1891.
[2]) NOTES ON NEW REMEDIES, February, 1892.
[3]) *Loc. citat.*
[4]) *Loc. citat.*
[5]) *Loc. citat.*
[6]) *Loc. citat.*
[7]). NOTES ON NEW REMEDIES, Vol. IV, p. 27, 1891.

Exp. II, for which a dog weighing 12.6 kilos was used, gave practically the same results. For Exp. III a dog weighing 18.14 kilos was selected. The first injection of 16 cc. was followed by a reduction of pressure, but this soon recovered completely. A second dose of the same amount, administered eight minutes later, produced a fall which was progressive up to death. The respiration was decreased in rate and shallow in character; it soon ceased under the second dose. The temperature was only slightly influenced; it had only fallen 0.7 of a degree at the time of the injection of the second dose.

EXPERIMENT IV. *Normal.*

Time Min.	Time Sec.	Dose Grammes	Pulse per Min.	Pressure M.M.	Respiration per Min.	Remarks. Dog Wgt 15.2 kilos.
0			96	140		41. *Phenocoll* Solution 1 per cent.
2	20	20cc.	105	142		Inj. begun.
3	10		123	110		Inj. ended.
4	10		131	150		
5	00	20cc.	114	156		Inj. begun.
6	00		129	160		Inj. ended.
6	30		150	170		
7	10	10cc.	144	160		Inj. begun.
7	50		144	160		Inj. ended.
13	50		120	160		40.9. Struggles.
15	30	30cc.	126	156		Inj. begun.
17	00		90	160		Inj. ended; pulse waves large.
17	50		129	160		
23	20	40cc.	135	160		Inj. begun.
25	10		108	140		Inj. ended.
25	50		129	170		
28	20		144	176		41.
32	10	30cc.	156	170		Inj. begun.
33	10		120	140		Inj. ended.
34	00		144	170		
39	40	20cc.	105	160		Inj. begun.
40	10		168	140		Inj. ended.
40	50		144	180		41.5
46	20	10cc.	174	170		4 per cent. Solution used; inj. begun.
46	40		126	140		Inj. ended.
47	00	10cc.	168	160		4 per cent. Solution used; inj. begun.
47	20		150	120		Inj. ended.
47	40	10cc.	120	140		Inj. begun of 4 per eent. Solution.
48	00		120	160		Inj. ended.
48	20		126	66		
48	40		114	160		41.8. Respir. stopped.
49	10		142	230		Pulse irregular; from this time pressure went down gradually till heart ceased.

A 1% solution of phenocoll was used for other experiments of which Exp. IV is an example. The animal used here weighed 15.2 kilos. An injection of 20 cc. caused a momentary fall of pressure which was soon recovered from. The column of mercury was then raised above the normal height, so that about 1½ minutes after the second dose of the same amount, the pressure

EXPERIMENT V. *Curarized.*

Time Min.	Time Sec.	Dose Grammes	Pulse per Min.	Pressure M.M.	Respiration per Min.	Remarks. Dog Wgt. 13.152 kilos.
0			186	150		*Phenocoll* Solution 4 per cent. Waited 20 minutes.
0	30	10cc.	186	150		Inj. begun.
1	50		186	110		
1	20		165	50		Inj. ended.
2	10		144	70		
4	40		189	130		Inj. begun.
5	30	10cc.	168	60		Inj. ended.
6	20		165	90		
9	50	10cc.	204	130		Inj. begun.
10	10		168	60		Inj. ended.
11	00		153	80		The last dose of 10cc. was followed by the same results and the animal died under it.

EXPERIMENT VI. *Vagi Cut.*

Time Min.	Time Sec.	Dose Grammes	Pulse per Min.	Pressure M.M.	Respiration per Min.	Remarks. Dog Wgt. 9.514 kilos.
0			192	150	27	39.3. *Phenocoll* Solution 4 per oent.
0	30	5cc.	192	150	27	Inj. begun.
1	00		165	100	27	Inj. ended.
1	50		156	130	24	
5	20	5cc.	174	150	15	Inj. begun.
5	50		171	100	15	Inj. ended.
11	50		126	130	21	38.9.
19	20	5cc.	123	136	18	Inj. begun.
20	00		120	90	24	Inj. ended.
20	00		105	120	21	Pulse waves large.
27	30	10cc.	96	140	15	38.8. Inj. begun.
28	20		105	72	15	Inj. ended.
33	50		114	128		38.0. Killed afterwards with ether.

EXPERIMENT VII. *Cord and Vagi Cut.*

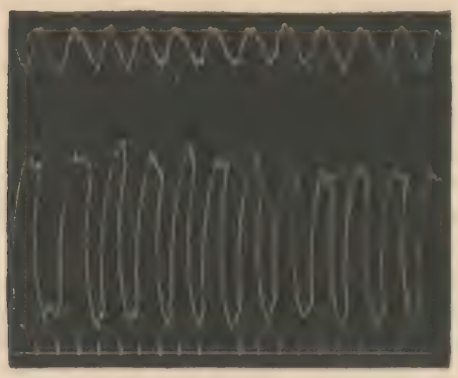
Time Min.	Time Sec.	Dose Grammes	Pulse per Min.	Pressure M.M.	Respiration per Min.	Remarks. Dog Wgt. 19 kilos.
0			186	14		*Phenocoll* Solution 5 per cent.
1	00	10cc.	186	14		Inj. begun.
1	50		144	8		Inj. ended.
2	50		117	6		
3	50		111	6		
4	50		120	8		
10	20	10cc.	126	8		Inj. begun.
11	00		120	4		Inj. ended; animal died 2 minutes later.

marked 170 mm., the normal being 140 mm.; it remained above this point under subsequent injections, but finally fell under three doses of 10 cc. each of a 4% solution. At the time of the stoppage of the respiration the needle of the manometer marked 230 mm., this perhaps being due to asphyxia. The temperature fell 0.1 of a degree after 50 cc. of the 1% solution had been ingested, but it went back to normal, and even rose to 0.8 above the normal before death; the animal died from respiratory failure.

FIG. h. (Normal).

PHENOCOLL.—Tracing of Dog, weighing 12.6 kilos. Injected into jugular vein 5cc. of a 1 per cent. solution of drug. Curves in centre represent the respiratory movements

FIG. i. (Normal).



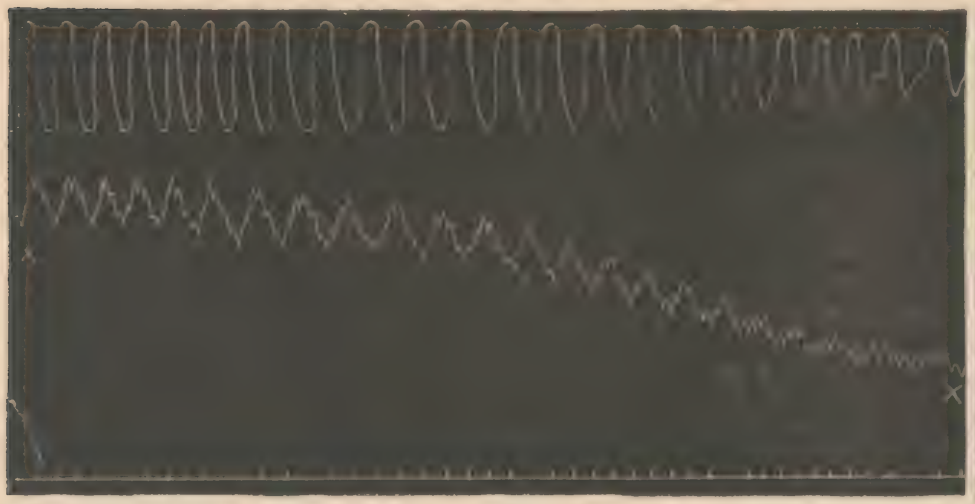
PHENOCOLL.—The same, 3 minutes after injection. No other changes occurred in over half an hour.

FIG. k. (Normal).

PHENOCOLL.—The same, 6 minutes after injection.

The action of phenocoll upon the arterial pressure, in medicinal doses, although slightly stimulating, is practically unimportant. The more marked effect, especially when comparatively large quantities are ingested, is that of depression, such phenomenon occurring similarly not only in curarized animals, but also in those in which section of the spinal cord and the pneumogastrics has been practiced beforehand. These results and the significant elevation of the reduced pressure by asphyxia, as is seen in the latter part of Exp. IV, all would seem to show that the vaso-motor system is not influenced by the drug.

FIG. j. (Normal).



PHENOCOLL.—Tracing of Dog, weighing 10.2 kilos. Injected into jugular vein 10cc. of a 4 per cent. solution of drug, between x—x marks. Uppermost curves represent respiratory movements.

FIG. l. (Normal).

PHENOCOLL.—The same, 9 minutes later

Fig. m. (Vagi Cut).

PHENOCOLL.—Tracing of Dog, weighing 6.5 kilos. Injected intravenously 5cc. of a 4 per cent. solution of drug.

Fig. n. (Vagi Cut).

PHENOCOLL.—The same, 4 minutes after injection.

The Pulse.—The heart-beat in the normal animal was at first diminished, the reduction being generally followed by an increase above the original rate. The same result was noticed in curarized dogs. The rapidity of the pulse was prevented by previous section of the vagi and of all the nerves supplying the heart, as is observed in Exp. VII. It may be inferred from such results that the primary reduction of the pulse-rate is due to stimulation of the cardio-inhibitory centres; the secondary quickening to paralysis of the same. A further proof of this last assertion is found in Exp. II, in which electrical irritation of the central end of a vagus produced no effect. The final diminution of the pulse-rate, which was often accompanied by a marked increase in the size of the pulse-waves, may be said to be due to an action upon the heart.

The Blood.—As far as we have been able to observe, phenocoll exercises no action upon this tissue.

Conclusions.—We conclude, then, that

1. Phenocoll, in ordinary amounts, has practically no effect upon the circulation.

2. Large doses diminish the blood-pressure by influencing the heart.

3. Phenocoll reduces the pulse-rate by stimulating the cardio-inhibitory centres. It then increases the rapidity of the pulse by paralyzing said centres. The final diminution is of cardiac origin.

4. Upon the blood itself phenocoll has no action.

On Heat Phenomena.

The manner in which antipyretics act on temperature is imperfectly understood. It seems to be the general concensus of opinion that they act through the nervous mechanism controlling the temperature of the body. Sawadowski, quoted by Ott [1]), has failed to get the usual effect of antipyrine after destruction of the corpora striata. This has been confirmed by Ott [2]).

Nearly all experimenters have failed to get with normal animals the decided action obtained with fevered animals. This fact signifies that metabolism is not affected directly, or we would have a constant action on heat phenomena.

We shall study in this paper the effect of antipyrine, phenacetine and phenocoll on the normal animal and then on an animal in a state of fever.

The experiments have been made with the ordinary calorimeter described by Reichert [3]). The animals were all healthy dogs, which had been fed the night previous to the experiment and not allowed to eat or drink during the course of the experiment. The heat production (H.P.) and the heat dissipitation (H.D.) were measured for periods of one hour. The normal H.P. and H.D. were taken for two hours, and then the drug given, and the heat production and heat dissipitation observed for three hours more. In the normal animals the drugs were injected subcutaneously. In studying the results obtained we must not be too hasty to say slight changes result from the drug. In the first place it must be borne in mind that the heat production and heat dissipitation vary a great deal from hour to hour normally. Further, Reichert [4]) has shown that confinement in a box for several consecutive hours causes a fall of animal temperature.

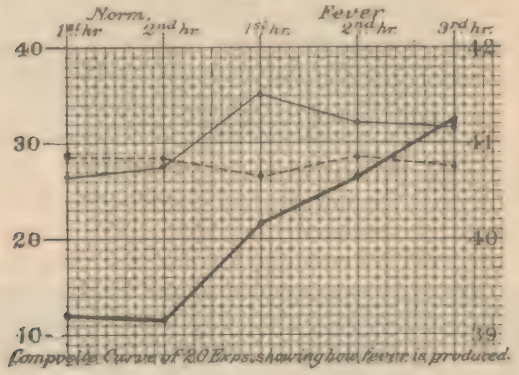
Before we can study the effect of antipyretics on fevered animals, we must try to determine how the fever is produced. Most of our experimental fevers

[1]) Modern Antipyretics, 1891.
[2]) *Loc. citat.*
[3]) University Medical Magazine, January, 1890.
[4]) University Medical Magazine, February, 1890.

were produced by intravenous injection of putrid blood. The subcutaneous injection of both putrid blood and albumoses failed to produce an immediate fever. The method of injecting one large dose of putrid blood is very undesirable because it causes an intense fever, whose maximum is soon reached and then gradually falls. In the experiments given in this paper the blood was injected every hour in 5 drop doses, after the normal temperature had been taken for two hours. This produced a steady fever. On the second day, the same dog, under the same circumstances, was placed in the calorimeter and his H.P. and H.D. taken; then after that, 5 drops of putrid blood were again injected every hour. After the first hour of fever the drug was given by the stomach, in order that the relative time of absorption might be determined.

The fever was produced the first day by an increase of the H.P. We give below a composite curve showing how fever was produced in twenty experiments. It will be seen that with H.D. there was scarcely any disturbance; but the H.P. rises enormously at first, causing the elevation of temperature. After the fever is established, the heat production falls although the temperature continues to rise, because the H.P. is constantly in excess of the H.D.

FIG. o.



ANTIPYRINE.

We tabulate below the results of antipyrine on normal animals:

ANTIPYRINE IN NORMAL ANIMALS.

HEAT PRODUCTION.

No. of Exp.	Wgt p. kilo.	Before inj. 1st hour.	Dose Sub. p. kilo	After injection. 1st h.	2nd h.	3rd h.	4th h.	5th h.
I.	10.54	20.56	0.1 grm.	10.41	17.51	16.42	9.95	13.22
II.	13.37	28.97	0.1 "	28.64	27.31	32.04	28.25	29.64
III.	5.10	19.56	0.1 "	22.53	24.00	21.17	24.50	20.89
IV.	11.66	36.96	0.1 "	31 76	30.89	30.68	31.35	27.63
V.	11.55	26.87	0.1 "	24.84	27.75	24.31	24.04	24.40
VI.	12.92	25.91	0.25 "	31.07	25.84	26.93	22.31	28.62
VII.	12.81	23.41	0.4 "	25.63	27.32	19.74	16.28	14.67
VIII.	10.99	10.87	0.4 "	13.86	15.85	16.09	18.97	13.77
Average		24.14		23.59	24.50	23.42	21.96	21.61

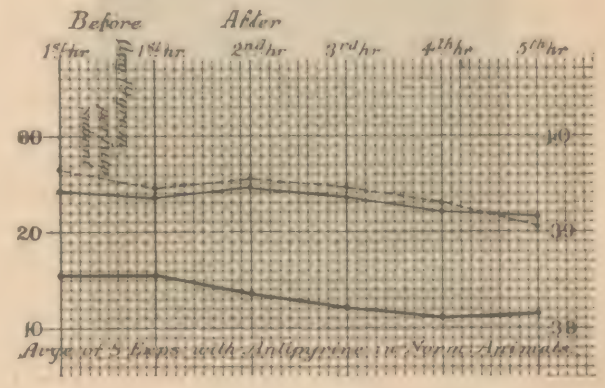
HEAT DISSIPATION.

I.	21.32	16.82	17.17	15.75	12.15	13.22
II.	30.51	29.07	29.45	32.15	29.00	28.77
III.	20.95	22.77	24.57	22.15	24.17	20.45
IV.	38.00	30.27	33.22	29.92	31.82	26.42
V.	28.26	25.86	28.12	25.42	24.22	24.40
VI.	28.55	29.70	27.00	27.20	24.95	23.35
VII.	27.82	26.67	27.42	23.02	17.10	14.16
VIII.	15.45	16.15	16.65	20.22	18.62	15.97
Average	26.42	24.66	25.45	24.48	22.75	20.84

TEMPERATURES.

I.	38.8	38.1	38.1	38.2	37.9	37.9
II.	38.3	38.3	38.1	38.1	38.1	38.3
III.	38.8	38.8	38.7	38.4	38.5	38.6
IV.	38.3	39.5	38.2	38.3	38.3	38.4
V.	38.4	38.3	38.3	38.2	38.1	38.1
VI.	38.4	38.6	38.4	38.3	38.1	38.1
VII.	38.5	38.3	38.3	37.9	37.9	37.9
VIII.	38.8	38.6	38.7	38.2	38.2	38.0
Average	38.54	38.56	38.85	38.20	38.13	38.16

FIG. p.



Above is seen a compositive curve showing the effects of antipyrine in the normal animal. The numerals to the left represent heat-units. The continuous line represents heat production, and the dotted line heat dissipation. The curve below (continuous *heavy black* line) represents the temperature in degrees centigrade.

We see here a slight fall of temperature for three hours after the drug was given. This occurs with a corresponding fall in H.P. and H.D., all of which was so slight that we cannot say that the whole change would not have occurred without any drug, as the result of the animals being confined in the calorimeter for several consecutive hours.

The effect of antipyrine in fever is seen in the following table:

ANTIPYRINE IN FEVER.

HEAT PRODUCTION.

No. of Exp.	Wgt. in kilos.	First Day. In normal state. 1st h.	2nd h.	Dose of p. blood. p. hour.	In fever state (no drug) 1st h.	2nd h.	3rd h.	Second Day. Normally.	Dose of p. blood. p. hour.	In fever.	Dose of Antipyrine p. kilo.	After drug. 1st h.	2nd h.	3rd h.
I.	9.62	33.11	29.00	5 drops	47.77	34.42	27.58	21.00	5 drops	37.03	1.86 grm.	23.54	12.70	20.91
II.	9.29	21.05	23.17	5 "	43.10	34.08	34.86	26.51	5 "	35.84	0.93 "	44.97	25.62	15.37
III.	9.07	21.77	21.82	5 "	29.05	26.73	24.29	19.26	5 "	33.30	0.93 "	30.48	32.63	Death.
IV.	12.34	26.00	27.28	5 "	29.74	38.94	37.16	25.25	5 "	30.76	0.41 "	17.66	25.48	23.66
V.	12.13	28.39	27.44	5 "	28.30	30.47	32.33	28.10	5 "	45.24	0.41 "	27.15	31.31	21.47
Average	10.49	26.06	25.74		35.59	32.93	31.24	24.02		36.43	0.93 grm.	28.76	25.55	20.35

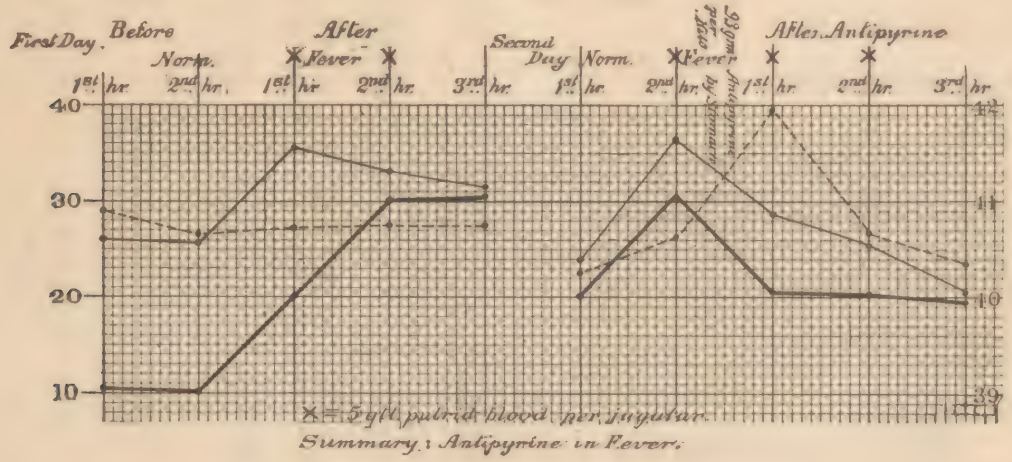
HEAT DISSIPATION.

	First Day.					Second Day.				
I.	34.63	30.15	30.45	35.57	28.35	24.08	20.86	35.86	23.43	19.37
II.	24.75	26.87	34.22	28.90	30.42	25.07	27.15	50.77	28.52	22.62
III.	23.25	22.19	19.80	18.59	22.81	19.29	22.89	35.55	24.30	Death.
IV.	28.50	25.75	25.74	28.44	31.16	25.25	27.31	36.90	32.88	26.62
V.	33.79	28.34	25.60	25.57	24.23	29.07	32.15	39.37	25.49	25.35
Average	28.98	26.67	27.16	27.41	27.39	22.53	26.07	39.69	26.93	23.49

TEMPERATURES.

	First Day.					Second Day.				
I.	39.4	39.25	41.5	41.7	41.6	39.2	41.3	39.7	38.3	38.5
II.	39.4	38.9	40.1	40.8	41.4	40.5	41.7	40.9	40.5	39.5
III.	39.2	39.16	40.4	41.5	41.7	40.5	41.95	41.25	42.4	Death.
IV.	39.25	39.4	39.8	40.85	41.45	40.5	41.85	39.9	39.15	38.85
V.	39.4	39.3	39.6	40.3	41.2	40.3	41.65	40.4	41.0	40.6
Average	39.13	39.2	40.28	41.03	41.47	40.2	41.69	40.43	40.27	39.36

FIG. 9.



Summary. Antipyrine in Fever.

An examination of the results obtained from the experiments with antipyrine in fever shows that the fever is produced the first day by an increase of heat production without any alteration in the heat dissipation. This increase is greatest the first hour, and the temperature continnes to rise although the heat production falls some after the fever is established.

The second day we see the fever produced again, as on the previous day, by an increase of heat production. But the very next hour, after the administration of antipyrine by the stomach, we observe in the composite curve a fall of 1.2.° C., produced by a double action: an increase of heat dissipation and a reduction of heat production. The fall of temperature continues till the end of the experiment. It would seem from this that antipyrine, to cause this double action, must influence the *thermotaxic* mechanism.

PHENACETINE.

Very little experimental work has been done with phenacetine. OTT [1]) has studied the effect of this drug on the heat functions and concludes that phenacetine reduces the temperature by causing a fall of both heat production and heat dissipation.

[1]) Journal of Nervous and Mental Diseases, 1888, p. 598.

An examination of our experiment with phenacetine in normal animals shows practically no changes. There is a slight fall of temperature the third hour after the drug was given, but so slight that it cannot be said to be due to the effect of the remedy.

In the fever experiments we see again the fever produced by an increase of H.P. On the second day we notice in the average of the results a decrease of ten heat units in the heat production during the first hour after the administration of the drug per stomach. The temperature, however, does not fall much until the third hour; and the heat production reaches the minimum at this time. The H.D. is very slightly affected. It would, therefore, seem that phenacetine does not act as promptly as antipyrine, and that it causes a fall of temperature by producing a diminution of heat production. In order to see if phenacetine would act differently in a fever produced in another manner the following experiments were performed:

EXPERIMENT A.—Dog-weight, 10.31 kilos.

FIRST DAY.

	H.P.	H.D.	TEMP.
First hour	20.00	24.94	39.0
0.267 gram. Albumose per jugular.			
Second hour	44.64	24.43	41.45
0.267 gram. Albumose per jugular.			
Third hour	31.85	26.05	42.15
No injection.			
Fourth hour	28.07	26.32	42.35

SECOND DAY.—Animal reduced to 10.09 kilos

First hour	19.26	24.10	39.0
0.2 gram. Albumose per jugular.			
Second hour	35.06	22.15	40.9
0.2 gram. Albumose per jugular, and 4.8 gram. Phenacetine per stomach, (0.48 gram. per kilo).			
Third hour	21.87	23.88	40.05
0.2 gram. Albumose per jugular.			
Fourth hour	26.01	24.00	40.9
0.2 gram. Albumose per jugular.			
Fifth hour	21.17	26.81	40.2

EXPERIMENT B.—Dog-weight 11.55 kilos.

FIRST DAY.

	H.P.	H.D.	TEMP.
First hour	34.22	36.99	39.4
Second hour	36.61	38.45	39.2
0.2 gram. Albumose per jugular.			
Third hour	41.76	34.37	40.0
0.2 gram. Albumose per jugular.			
Fourth hour	37.20	32.14	40.55
0.2 gram. Albumose per jugular.			
Fifth hour	34.28	28.30	41.2

SECOND DAY.—Animal reduced to 10.88 kilos.

First hour	25.63	22.59	40.95
0.2 gram. Albumose per jugular, and 5.2 gram. Phenacetine per stomach.			
First hour after the ingestion of drug	33.39	31.21	41.85
0.2 gram. Albumose per jugular.			
Second hour after drug	27.52	30.43	41.3
0.2 gram Albumose per jugular.			
Third hour after drug	24.70	26.87	41.05
0.2 gram. Albumose per jugular.			
Fourth hour after drug	22.21	26.90	40.5
0.2 gram. Albumose per jugular.			
Fifth hour after drug	21.99	28.08	39.8

It will be seen from this that albumoses produce fever also by a rise of heat production, and that phenacetine keeps the temperature from rising to the height attained during the first day, by diminishing the heat production. The heat dissipation is not affected by the drug.

We append the following tables showing the actions of phenacetine on normal and fevered animals:

PHENACETINE IN NORMAL ANIMALS.

HEAT PRODUCTION.

No. of Exp.	Wgt. in kilos.	Before injection. 1st h.	Before injection. 2nd h.	Dose Sub p. kilo.	After injection. 1st h.	After injection. 2nd h.	After injection. 3rd h.
I.	10.21	32.63	26.21	0.1 grm.	24.96	22.92	20.47
II.	9.51	20.93	23.78	0.1 "	23.41	22.50	——
III.	9.07	47.08	47.01	0.1 "	49.37	41.91	39.94
IV.	12.92	35.94	32.59	0.1 "	32.64	30.72	31.97
V.	9.51	28.28	26.06	0.1 "	26.72	24.40	17.01
Average	10.24	32.97	31.13	0.1 grm.	31.42	28.45	27.35

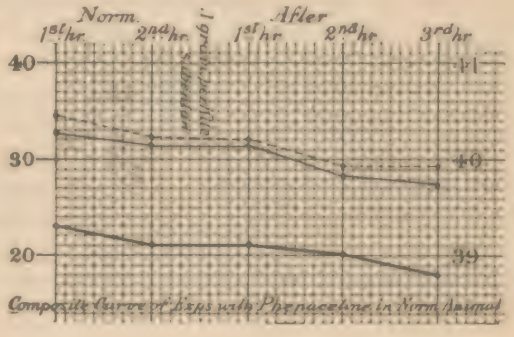
HEAT DISSIPATION.

I.	35.07	28.00	25.45	25.98	22.10
II.	20.17	24.92	24.55	22.50	——
III.	47.80	48.45	47.92	42.27	41.75
IV.	40.07	34.65	34.70	30.72	33.00
V.	29.80	25.30	27.10	24.02	20.05
Average	34.58	32.26	31.96	29.19	29.22

TEMPERATURES.

I.	39.4	39.2	39.1	38.7	38.5
II.	39.1	38.95	38.8	38.8	——
III.	39.3	39.1	39.3	39.25	39.0
IV.	39.0	38.8	38.6	38.6	38.5
V.	39.5	39.6	39.55	39.6	39.2
Average	39.3	39.1	39.1	39.0	38.8

FIG. 1.



PHENACETINE IN FEVER.

HEAT PRODUCTION.

No. of Exp.	Wgt. in kilos.	First Day. In normal state. 1st h.	2nd h.	Dose of p. blood. p. hour.	In fever state (no drug) 1st h.	2nd h.	3rd h.	Second Day. Normally	Dose of p. blood. p. hour.	In fever	Dose of Phenacetine. p. kilo.	After drug. 1st h.	2nd h.	3rd h.
I.	8.16	21.64	22.97	5 drops	26.29	24.11	26.96	16.98	5 drops	28.92	0.48 grm.	19.53	27.48	22.21
II.	9.26	20.40	33.42	5 "	27.37	30.55	24.36	25.91	5 "	42.21	0.48 "	29.60	33.88	23.06
III.	10.23	36.81	32.45	5 "	41.09	44.01	44.58	28.76	5 "	40.12	0.48 "	35.87	39.29	24.52
IV.	10.83	29.21	32.34	5 "	43.87	27.78	39.24	25.98	5 "	48.88	0.48 "	28.69	35.74	32.41
V.	10.23	19.67	17.90	5 "	28.14	24.49	——	20.42	5 "	29.00	0.48 "	22.76	25.56	17.19
Average	9.62	25.55	27.81		33.35	30.18	33.78	23.61		37.82	0.48 grm.	27.29	32.39	23.87

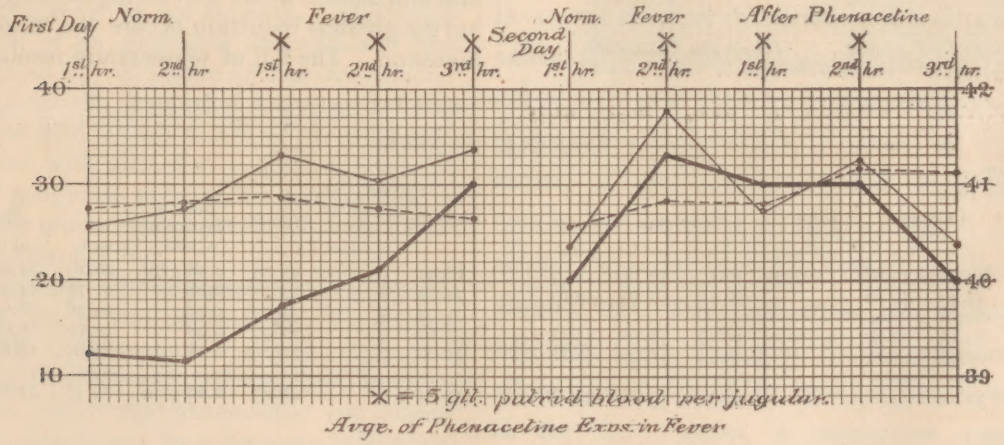
HEAT DISSIPATION.

	First Day.					Second Day.				
I.	20.67	24.27	23.03	18.90	21.10	18.93	22.40	23.76	25.20	27.42
II.	21.95	33.05	26.25	30.55	22.86	26.65	30.84	28.86	34.26	33.42
III.	39.42	32.88	37.08	40.10	25.45	32.46	33.58	31.38	40.10	35.15
IV.	32.93	33.58	35.60	27.78	35.94	30.07	32.93	34.82	38.19	33.22
V.	22.55	17.90	21.96	19.14	——	21.23	21.23	21.13	21.88	27.00
Average	27.50	28.33	28.78	27.29	26.33	25.89	28.19	27.99	31.92	31.24

TEMPERATURES.

	First Day.					Second Day.				
I.	39.4	39.2	39.7	40.5	41.4	40.8	41.8	40.15	40.5	39.7
II.	39.2	39.25	39.4	39.4	41.4	39.4	40.95	41.05	41.0	39.6
III.	38.9	38.85	39.3	39.75	40.08	40.25	41.05	41.6	41.5	40.2
IV.	39.35	39.2	40.2	40.2	40.6	39.7	41.65	40.9	40.6	40.5
V.	39.25	39.25	40.0	40.65	——	40.1	41.05	41.25	41.7	40.5
Average	39.2	39.15	39.7	40.1	41.05	40.05	41.3	40.99	41.06	40.1

FIG. 8.



Avge. of Phenacetine Exps. in Fever

PHENOCOLL.

As far as we know no calorimetrical studies have been made with phenocoll.

An examination of our experiments with this drug in normal animals shows that it exercises no effect on the heat functions. There is a slight fall of temperature at the end of the experiments, but this is so slight that it is probably the result of the animal being kept in the calorimeter for several consecutive hours, and not that of the action of the drug.

The following experiments given in tabular form sufficiently explain themselves:

PHENOCOLL IN NORMAL ANIMALS.

HEAT PRODUCTION.

No. of Exp.	Wgt. in kilos.	Before injection 1st h.	2nd h.	Dose Sub. p. kilo.	After injection. 1st h	2nd h.	3rd h.
I.	7.7	23.46	24.19	0.15 grm.	17.94	19.11	——
II.	8.61	18.25	20.60	1.5 "	26.00	24.18	22.57
III.	13.60	57.31	44.98	2.0 "	34.84	38.49	——
IV.	7.25	16.60	23.41	1.5 "	20.22	19.95	——
V.	10.23	23.75	34.91	1.6 "	31.95	26.58	32.61
Average	9.88	27.87	29.61	1.25 grm.	26.19	25.64	27.59

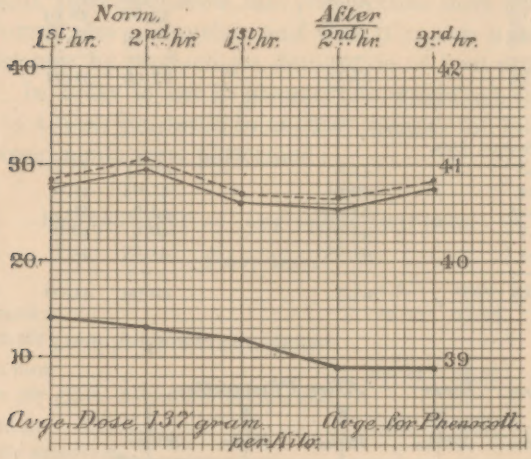
HEAT DISSIPATION.

I.	25.30	24.80	20.40	18.50	——
II.	19.62	21.97	25.32	22.12	23.25
III.	51.87	47.15	37.00	39.57	——
IV.	16.60	22.25	23.12	22.75	——
V.	28.65	35.72	29.50	29.85	33.42
Average	28.46	30.37	27.07	26.56	28.33

TEMPERATURES.

I.	39.1	39.0	38.6	38.7	——
II.	39.4	39.2	39.3	39.0	39.1
III.	40.0	39.8	39.6	39.5	——
IV.	39.4	39.6	39.1	38.6	——
V.	39.1	39.1	39.3	38.9	38.8
Average	39.4	39.3	39.2	38.9	38.9

FIG. t.



The experiments on fevered animals show a decided action of phenocoll on the animal temperature. The fever was produced as before by an increase of heat production. The diminution in heat dissipation with the beginning of fever in these experiments was caused by the unusual results in Exp. IV. On the second day there was an enormous rise of heat production with the introduction of putrid blood. The next hour after the administration of phenocoll by the stomach the temperature fell almost to the normal, and continued falling during the rest of the experiment. This fall of temperature was caused by a corresponding diminution of heat production. The heat dissipation is not affected.

CONCLUSIONS.

1. Antipyrine, Phenacetine and Phenocoll all fail to produce any effect on the heat functions of the normal animal.

2. Antipyrine produces a decided fall of temperature in the first hour after its administration in the fevered animal. This reduction is due to a great increase in heat dissipation, together with a fall in the heat production.

3. Phenacetine, both in septic and albumose fevers, produces a very slight fall of temperature during the first and second hours after its ingestion by the stomach, but the greatest reduction occurs the third hour after its ingestion. The fall of temperature results chiefly from

PHENOCOLL IN FEVER.

HEAT PRODUCTION.

No. of Exp.	Wgt. in kilos.	First Day. In normal state. 1st h.	2nd h.	Dose of p. blood. p. hour.	In fever state (no drug) 1st h.	2nd h.	3rd h.	Second Day. Normally	Dose of p. blood. p. hour.	In fever.	Dose of Phenacetine p. kilo.	After drug. 1st h.	2nd h.	3rd h.	4th h.
I.	11.66	22.30	25.88	5 drops	48.17	36.28	31.95	18.99	5 drops	45.79	0.28 grm.	26.19	24.21	21.30	24.26
II.	12.13	47.49	43.24	5 "	56.56	56.36	49.61	34.79	5 "	61.21	0.28 "	11.77	54.02	39.22	28.22
III.	11.11	Same dog as in Experiment II.						31.27	5 "	55.71	0.28 "	29.76	38.64	30.43	——
IV.	10.23	23.15	29.87	5 drops	19.20	35.16	23.54	33.16	5 "	51.27	0.28 "	34.50	27.68	23.30	——
V.	38.38	35.58	35.21	5 "	29.44	31.76	32.88	21.00	5 "	26.29	0.28 "	24.65	18.85	12.57	——
Average	10.70	32.22	33.55		38.34	39.88	34.49	27.84		48.05	0.28 grm.	25.37	32.88	25.36	26.24

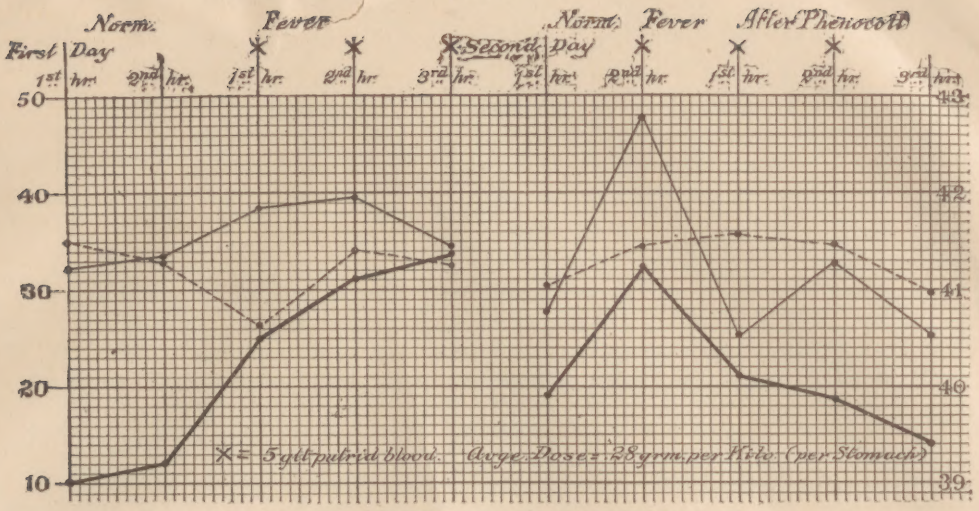
HEAT DISSIPATION.

	First Day.					Second Day.				
I.	27.95	26.35	27.90	32.52	34.77	20.85	28.55	39.70	29.80	27.35	27.05
II.	55.10	45.27	41.85	44.20	50.62	37.70	43.75	30.20	48.20	39.70	36.95
III.	Same dog as in Experiment II.					34.82	40.75	47.80	37.32	35.75	——
IV.	24.32	29.87	13.07	31.01	15.68	34.38	36.55	43.08	38.08	25.75	——
V.	32.93	30.88	23.40	28.40	29.52	23.68	23.28	18.29	20.52	20.95	——
Average	35.07	33.09	26.55	34.03	32.51	30.28	34.56	35.81	34.78	29.90	32.00

TEMPERATURES.

	First Day.					Second Day.					
I.	39.1	39.05	41.2	41.6	41.3	39.35	41.2	39.75	39.15	38.5	28.2
II.	39.15	38.95	40.4	41.6	41.5	39.6	41.4	39.5	40.1	40.05	39.15
III.	——	——	——	——	——	39.9	41.6	30.05	39.7	39.6	——
IV.	39.2	39.2	39.95	40.45	41.35	39.6	41.4	40.35	39.2	38.9	——
V.	38.95	39.6	40.5	41.0	41.5	40.1	40.55	41.5	41.25	40.00	——
Average	39.1	39.2	40.5	41.1	41.4	39.91	41.23	40.13	39.88	39.42	38.67

FIG. v.



Average of 5 Experiments with Phenocoll.

a decrease in heat production, with a slight increase in the heat dissipation. The increase in dissipation is not as great as with antipyrine. Probably the delayed action of the drug depends on its insolubility.

4. Phenocoll causes in fever a very decided fall in temperature, which occurs the first hour after the administration of the drug by the stomach. This reduction is the result of an enormous diminution of heat production, without any alteration of heat dissipation.

Our experiments with antipyrine are in accord with the results obtained by MARTIN [1]). WOOD, REICHERT and HARE [2]), together with DESTREE [3]), have reached the conclusion that antipyrine reduces the temperature by a decrease in heat production, and that heat dissipation also falls with the production.

In our experiments with antipyrine the composite curve shows the rise of heat dissipation. We believe, therefore, that this phenomenon is effected through a *thermotaxic* rather than through a *thermogenic* mechanism. We further believe that phenacetine and phenocoll reduce the temperature by a decrease in the heat production through their action on a *thermogenic* nervous centre. The fact that all drugs here studied fail to produce any effect on the normal heat function proves that they affect these functions through the nervous system. Probably the fact pointed out by HARE in his excellent essay [4]) that many investigators do not take into account other circumstances, such as tying animals down, and confinement in a box, may explain many of the results obtained by some observers in the normal animal.

In concluding this study we are justified, judging from the results of our experimentation, in saying that of the three drugs in question, the safest for practical purposes, especially as regards an action upon abnormal temperatures, would be phenocoll. Phenacetine is slow on account, no doubt, of its insolubility, and is comparatively feeble as antipyretic. Antipyrine, it is true, is soluble and prompt in reducing feverish conditions, but its action upon the circulation, particularly upon the heart, is so pronounced, even when administered in therapeutic doses, that it is, for this reason, a dangerous substance to use. Phenocoll, on the other hand, is readily soluble, rapidly absorbed, and, undoubtedly, promptly eliminated. Its power to reduce abnormal high temperatures is very decided, and it does this in therapeutic doses, without depressing the circulation. Phenocoll, therefore, would seem to be superior to antipyrine and phenacetine as an antipyretic.

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1) Therapeutic Gazette, 1887.
2) Therapeutic Gazette, Vol. II, p. 803.
3) Jour. de Medecine de Bruxelles, July 20, 1888.
4) Fever: Its Pathology and Treatment, Boylston Prize Essay, 1890.